

WHAT IS CLAIMED IS:

- 5 1. A pharmaceutical composition comprising a GLP-1 agonist and a gastrin compound that provides beneficial effects relative to each compound alone, and optionally a pharmaceutically acceptable carrier, excipient, or vehicle.
2. A pharmaceutical composition as claimed in claim 1 in a form that provides normal blood glucose levels in a subject that persist for a prolonged period of time after administration.
- 10 3. A pharmaceutical composition as claimed in any preceding claim comprising therapeutically effective amounts of a GLP-1 agonist and a gastrin compound in a form for chronic or acute therapy of a subject in need thereof.
4. A pharmaceutical composition as claimed in claim 3 wherein the therapeutically effective amounts are suboptimal relative to the amount of each compound administered alone for treatment of diabetes.
- 15 5. A pharmaceutical composition as claimed in any preceding claim wherein the ratio of GLP-1 agonist to gastrin compound is selected to augment the activity of the GLP-1 agonist or gastrin compound.
6. A pharmaceutical composition as claimed in claim 1 wherein the ratio of a GLP-1 agonist to a gastrin compound is from about 1:1 to 1:110, 1:1 to 1:100, 1:1 to 1:75, 1:1 to 1:50, 1:1 to 1:25, 1:1 to 1:10, 1:1 to 1:5, and 1:1.
- 20 7. A pharmaceutical composition as claimed in claim 1 wherein the ratio of a gastrin compound to a GLP-1 agonist is from about 1:1 to 1:110, 1:1 to 1:100, 1:1 to 1:75, 1:1 to 1:50, 1:1 to 1:25, 1:1 to 1:10, and 1:1 to 1:5.
8. A pharmaceutical composition as claimed in any preceding claim wherein the GLP-1 agonist is used in combination with the gastrin compound at therapeutically effective weight ratios of between about 1:1.5 to 1:150, preferably 1:2 to 1:50.
- 25 9. A pharmaceutical composition as claimed in any preceding claim wherein the GLP-1 agonist and the gastrin compound are present in doses that are at least about 1.1 to 1.4, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, or 10 fold lower than the doses of each compound alone required to treat a condition and/or disease.
10. A pharmaceutical composition as claimed in claim 1 comprising an additive amount of the GLP-1 agonist and the gastrin compound in a pharmaceutically acceptable excipient, carrier, or vehicle.
- 30 11. A pharmaceutical composition as claimed in claim 1 comprising a synergistically effective amount of the GLP-1 agonist and the gastrin compound in a pharmaceutically acceptable excipient, carrier, or vehicle.
12. A pharmaceutical composition as claimed in claim 1 comprising between 0.1 to 20, 0.1 to 30, 0.1 to 40, 0.1 to 50, and 0.1 to 60 micrograms/kg/day GLP-1 agonist and 0.1 to 20, 0.1 to 30, 0.1 to 40, 0.1 to 50, and 0.1 to 60 micrograms/kg/day gastrin compound.
- 35 13. A pharmaceutical composition as claimed in claim 2 wherein the beneficial effects are one or more of the following: reduced or absent islet inflammation, decreased disease progression, increased survival, or decreased symptoms of a disease or condition.

14. A pharmaceutical composition as claimed in any preceding claim wherein the beneficial effects are sustained beneficial effects that persist for a prolonged period of time after termination of treatment.
15. A pharmaceutical composition as claimed in claim 14 wherein the beneficial effects are sustained for at least about 2, 4, 5, 6, or 10 weeks, 2 to 4 weeks, 2 to 8 weeks, 2 to 12 weeks, 2 to 24 weeks, 2 weeks to 12 months, and 2 weeks to 18 months following treatment.
16. A pharmaceutical composition as claimed in claim 15 wherein the sustained beneficial effects may manifest as increased C-peptide production, increased pancreatic insulin production, and about normal or low blood glucose levels for a prolonged period following treatment.
17. A pharmaceutical composition as claimed in any preceding claim wherein the beneficial effect is at least about a 0.5%, 1%, 2%, 5%, 10%, 15%, 20%, 30%, 33%, 35%, 40%, 45%, or 50% increase in pancreatic insulin levels.
18. A pharmaceutical composition as claimed in any preceding claim wherein the beneficial effect is at least about a 2%, 5%, 10%, 15%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90% decrease in blood glucose levels.
19. A pharmaceutical composition as claimed in any preceding claim wherein the beneficial effect is a decrease in blood glucose levels for a period of at least 2, 4, 6, 8, or 10 weeks, 2 to 4 weeks, 2 to 6 weeks, 2 to 8 weeks, 2 to 12 weeks, 2 to 24 weeks, 2 weeks to 12 months, and 2 weeks to 18 months following treatment.
20. A pharmaceutical composition as claimed in any preceding claim wherein the GLP-1 agonist is a GLP-1(1-37), GLP-1(7-36) amide, fragments, analogues, and derivatives thereof, and active metabolites and prodrugs of GLP-1.
21. A pharmaceutical composition as claimed in any preceding claim wherein the GLP-1 is GLP-1(7-36) of SEQ ID NO. 5 or gastrin-17(leu) of SEQ ID NO. 14.
22. A pharmaceutical composition as claimed in any preceding claim wherein the GLP-1 agonist comprises a parent polypeptide of the formula GLP-1(7-R) wherein R is 36, 37, 38, 39, 40, 41, 42, 43, 44, and 45, and wherein optionally up to 5, 10, or 15 amino acid residues are replaced with any α -amino acid residue.
23. A pharmaceutical composition as claimed in any preceding claim wherein the GLP-1 agonist is an analogue or derivative of GLP-1 listed in Table 1.
24. A pharmaceutical composition as claimed in any preceding claim wherein the gastrin compound is gastrin 71 [SEQ ID NO. 15], gastrin 52 [SEQ ID NO. 16], gastrin 34 (big gastrin) [SEQ ID NO. 11 or 12], gastrin 17 (little gastrin) [SEQ ID NO. 13 or 14], gastrin 14 [SEQ ID NO. 17], gastrin 8, gastrin 6 [SEQ ID NO. 18 or 19], pentagastrin, and tetragastrin
25. A pharmaceutical composition as claimed in any preceding claim wherein the gastrin compound is a compound of the formula Z-Ym-Xn-AA1-AA2-AA3-AA4-AA5-AA6, wherein AA1 is Tyr or Phe, AA2 is Gly, Ala, or Ser, AA3 is Trp, Val, or Ile, AA4 is Met or Leu, AA5 is Asp or Glu, and AA6 is Phe or Tyr which is optionally amidated; Z is a carrier, preferably a polymer, more preferably a protein; Ym is an optional spacer region comprising m amino acid residues of a small neutral amino acid including but not limited to serine and alanine, and X is any consecutive portion of residues 1-28 of

- SEQ ID NO: 11 or 12, or residues 1-11 of SEQ ID NO. 13 or 14, preferably AA1-AA2-AA3-AA4-AA5-AA6 is Tyr-Gly-Trp-Met-Asp-Phe or Tyr-Gly-Trp-Leu-Asp-Phe.
26. A pharmaceutical composition of any preceding claims wherein the GLP-1 agonist is selected from the group consisting of Gly8-GLP-1(7-37), Val8GLP-1(7-37), Val8Asp22GLP-1(7-37), Val8Glu22GLP-1(7-37), Val8Lys22GLP-1(7-37), Val8His22 GLP-1(7-37), Arg34Lys26(Ne(g-Glu(Na-hexadecanoyl))) -GLP-1(7-37), Gly8-GLP-1(7-36) amide, Val8GLP-1(7-36) amide, Val8Asp22GLP-1(7-36) amide, Val8Glu22GLP-1(7-36) amide, Val8Lys22GLP-1(7-36) amide, and Val8His22 GLP-1(7-36) amide, and the gastrin compound is gastrin comprising SEQ ID NO. 11, 12, 13, 14, 17, or 18.
27. A pharmaceutical composition of any preceding claim wherein the GLP-1 agonist is Arg34Lys26(Ne(g-Glu(Na-hexadecanoyl))) -GLP-1(7-37) and the gastrin compound is 15Leu gastrin 17 [SEQ ID NO. 14].
28. A pharmaceutical composition of claim 27 wherein the gastrin compound is associated with a serum protein, preferably human serum albumin.
29. A method for preparing a stable pharmaceutical composition of a GLP-1 agonist comprising mixing a GLP-1 agonist, a gastrin compound, and a pharmaceutically acceptable carrier, excipient, or vehicle effective to physically stabilize the GLP-1 agonist and adapted to provide beneficial effects, preferably sustained beneficial effects.
30. A conjugate comprising a GLP-1 agonist linked to a gastrin compound to provide beneficial effects, in particular sustained beneficial effects.
31. A conjugate of claim 30 wherein the GLP-1 agonist is selected from the group consisting of Gly8-GLP-1(7-37), Val8GLP-1(7-37), Val8Asp22GLP-1(7-37), Val8Glu22GLP-1(7-37), Val8Lys22GLP-1(7-37), Val8His22 GLP-1(7-37), Arg34Lys26(Ne(g-Glu(Na-hexadecanoyl))) -GLP-1(7-37), Gly8-GLP-1(7-36) amide, Val8GLP-1(7-36) amide, Val8Asp22GLP-1(7-36) amide, Val8Glu22GLP-1(7-36) amide, Val8Lys22GLP-1(7-36) amide, and Val8His22 GLP-1(7-36) amide, and the gastrin compound is gastrin comprising SEQ ID NO. 11, 12, 13, 14, 17, or 18 optionally associated with a serum protein.
32. A method for treating or preventing a condition and/or disease in a subject comprising administering to the subject a therapeutically effective amount of a GLP-1 agonist and a gastrin compound, or a composition or conjugate of any preceding claim, to produce a sustained beneficial effect.
33. A method as claimed in claim 32 wherein the sustained beneficial effect is a decrease in blood glucose levels for a period of at least 2, 4, 6, 8, or 10 weeks, 2 to 4 weeks, 2 to 6 weeks, 2 to 8 weeks, 2 to 12 weeks, 2 to 24 weeks, 2 weeks to 12 months, and 2 weeks to 18 months following treatment.
34. A method of treatment comprising administering to a subject a therapeutically effective amount of at least one GLP-1 agonist in combination with administration of at least one gastrin compound which upon administration to a subject with symptoms of diabetes provides sustained beneficial effects.
35. A method as claimed in claim 34 wherein administration with of at least one GLP-1 agonist in combination with administration of at least one gastrin compound provides sustained beneficial effects of at least one symptom of diabetes.
36. A method as claimed in claim 34 or 35 wherein therapeutically effective amounts of the GLP-1 agonist and the gastrin compound are combined prior to administration to the subject.

37. A method as claimed in claim 34 or 35 wherein therapeutically effective amounts of the GLP-1 agonist and the gastrin compound are administered to the subject sequentially.
38. A method as claimed in any preceding claim wherein the therapeutically effective amounts of a GLP-1 agonist and a gastrin compound are synergistically effective amounts.
- 5 39. A method of preparing a stable pharmaceutical composition of a GLP-1 agonist comprising mixing a GLP-1 agonist, a gastrin compound, and a pharmaceutically acceptable carrier, excipient, or vehicle effective to physically stabilize the GLP-1 agonist and adapted to provide beneficial effects preferably sustained beneficial effects.
40. A method of treating a condition and/or disease comprising administering a GLP-1 agonist and a gastrin compound, or a composition or conjugate of any preceding claim with a plurality of cells to a subject
10 in need thereof to thereby produce beneficial effects, preferably sustained beneficial effects.
41. A method of any preceding claim wherein the condition and/or disease is dyslipidemia, hyperglycemia, severe hypoglycemic episodes, stroke, left ventricular hypertrophy, arrhythmia, bacteraemia, septicaemia, irritable bowel syndrome, respiratory distress syndrome, functional dyspepsia, diabetes,
15 catabolic changes after surgery, stress induced hyperglycemia, gastric ulcers, myocardial infarction, impaired glucose tolerance, hypertension, Alzheimer's disease and other central and peripheral neurodegenerative conditions chronic heart failure, fluid retentive states, metabolic syndrome and related diseases, and disorders and obesity.
42. A method of claim 40 or 41 wherein the condition and/or disease is diabetes.
- 20 43. A method for inducing islet neogenesis in a subject comprising contacting islet precursor cells with a GLP-1 agonist and a gastrin compound, or a composition, or conjugate of any preceding claim in a sufficient amount to increase proliferation of islet precursor cells in the subject thereby inducing islet neogenesis.
44. A method for expanding and differentiating stem cells into insulin secreting cells comprising contacting
25 the stem cells with an effective amount of a GLP-1 agonist and a gastrin compound or a composition or conjugate of any preceding claim.
45. A method of any preceding claim wherein the GLP-1 agonist is selected from the group consisting of Gly8-GLP-1(7-37), Val8GLP-1(7-37), Val8Asp22GLP-1(7-37), Val8Glu22GLP-1(7-37), Val8Lys22GLP-1(7-37), Val8His22 GLP-1(7-37), Arg34Lys26(Ne(g-Glu(Na-hexadecanoyl))) -GLP-1(7-37), Gly8-GLP-1(7-36) amide, Val8GLP-1(7-36) amide, Val8Asp22GLP-1(7-36) amide,
30 Val8Glu22GLP-1(7-36) amide, Val8Lys22GLP-1(7-36) amide, and Val8His22 GLP-1(7-36) amide, and the gastrin compound is gastrin comprising SEQ ID NO. 11, 12, 13, 14, 17, or 18 associated with a serum protein.
46. A method of any preceding claim wherein the GLP-1 agonist is Arg34Lys26(Ne(g-Glu(Na-hexadecanoyl))) -GLP-1(7-37) and the gastrin compound is 15Leu gastrin 17 [SEQ ID NO. 14].
- 35 47. Use of a composition comprising a combination of at least one GLP-1 agonist and at least one gastrin compound for the preparation of a medicament for the treatment of a condition and/or disease.
48. Use of a GLP-1 agonist for the manufacture of a medicament for the treatment of a condition and/or disease to be used in combination with a gastrin compound.

49. Use of claim 45 or 46 wherein the GLP-1 agonist is selected from the group consisting of Gly8-GLP-1(7-37), Val8GLP-1(7-37), Val8Asp22GLP-1(7-37), Val8Glu22GLP-1(7-37), Val8Lys22GLP-1(7-37), Val8His22 GLP-1(7-37), Arg34Lys26(Ne(g-Glu(Na-hexadecanoyl))) -GLP-1(7-37), Gly8-GLP-1(7-36) amide, Val8GLP-1(7-36) amide, Val8Asp22GLP-1(7-36) amide, Val8Glu22GLP-1(7-36) amide, Val8Lys22GLP-1(7-36) amide, and Val8His22 GLP-1(7-36) amide, and the gastrin compound is gastrin comprising SEQ ID NO. 11, 12, 13, 14, 17, or 18.
50. Use of any preceding claim wherein the GLP-1 agonist is Arg34Lys26(Ne(g-Glu(Na-hexadecanoyl))) -GLP-1(7-37) and the gastrin compound is 15Leu gastrin 17 [SEQ ID NO. 14].
51. Use of any preceding claim wherein the condition and/or disease is dyslipidemia, hyperglycemia, severe hypoglycemic episodes, stroke, left ventricular hypertrophy, arrhythmia, bacteraemia, septicaemia, irritable bowel syndrome, functional dyspepsia, respiratory distress syndrome, diabetes, catabolic changes after surgery, stress induced hyperglycemia, gastric ulcers, myocardial infarction, impaired glucose tolerance, hypertension, Alzheimer's disease and other central and peripheral neurodegenerative conditions chronic heart failure, fluid retentive states, metabolic syndrome and related diseases, and disorders and obesity.
52. A kit form of a composition or conjugate as claimed in any preceding claim.